

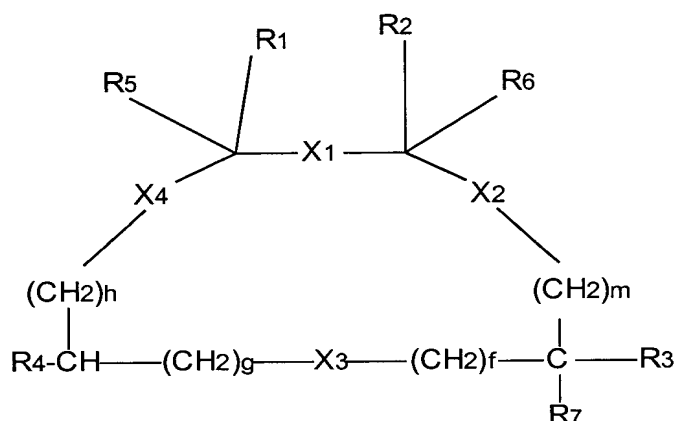


Version with Markings to Show Changes Made:

IN THE CLAIMS:

Kindly amend the Claims as follows:

1. (Amended twice) A monocyclic compound having the formula (I):



in which:

X_1, X_2, X_3, X_4 , which may be the same or different from one another, is selected from the group consisting of $-\text{CONR}-$, $-\text{NRCO}-$, $-\text{OCO}-$, $-\text{COO}-$, $-\text{CH}_2\text{NR}-$ and $-\text{NR-CH}_2-$, where R is H or a C_{1-3} alkyl or benzyl;

[f, g, h, m, which may be the same or different from one another, represent a number selected from the group consisting of 0, 1 and 2;

R_1 and R_2 , which may be the same or different from one another, represent a $-(CH_2)_r-$ Ar group, where $r = 0, 1, 2$ and where Ar is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar group being possibly substituted with a maximum of two residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxy, C_{2-4} amino-alkoxy, halogen, OH, NH_2 , and $NR_{13}R_{14}$ where R_{13} and R_{14} , which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_3 is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula C_nH_{2n+1} , with $n = 1-5$, cyclo-alkyl or alkylcyclo-alkyl groups having the formula C_nH_{2n+1} , with $n = 5-9$,

$-(CH_2)_r-Ar_1$ group, where $r = 0, 1, 2$ and where Ar_1 is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxy or amino-alkoxy, halogen, OH, NH_2 and $NR_{13}R_{14}$ where R_{13} and R_{14} , which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_4 is selected from the group consisting of:

-hydrogen or C_{1-6} alkyl,

-L-Q, where L is a chemical bond or a linear or branched C_{1-6} alkyl residue and Q is selected from the group consisting of:

i) H, OH, OR_9 , NH_2 , NR_9R_{10} , guanidine, sulfate, phosphonate and phosphate where R_9 and R_{10} , which may be the same or different from one another, represent a hydrogen C_{1-3} alkyl group, C_{1-3} hydroxyalkyl, C_{1-3} dihydroxyalkyl, C_{1-3} alkyl- $CONHR_{12}$, C_{1-3} alkyltetrazole, C_{1-3} alkyl-COOH or wherein R_9R_{10} joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom selected from the group consisting of N, O and S and wherein R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3} acyl groups or substituted with amino-groups or C_{1-3} acylamino-groups;

ii) COOH, tetrazole, SO₂NH₂, SO₂NHCOOR₈, CONHR₈, NHCOR₈, where R₈ represents a linear or cyclic C₁₋₆ alkyl chain containing one or more polar groups selected from the group consisting of: OH, NR₁₅R₁₆, COOH, CONHR₁₂, PO₃H and SO₃H, OR₁₁ and where R₁₅ and R₁₆, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group, and where R₁₁ is a C₁₋₃ alkyl or C₂₋₄ amino-alkyl chain, R₁₂ is a mono-, di-, tri-glycosidic group possibly protected with one or more C₁₋₃ acyl groups or substituted with amino-groups or C₁₋₃ acylamino-groups or R₁₅R₁₆ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C₁₋₃ alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) COOR₁₇, CONHR₁₂, OR₁₂ where R₁₂ is a mono-, di-, tri-glycoside group possibly protected with one or more C₁₋₃ acyl groups or substituted with amine or C₁₋₃ acylamine groups and R₁₇ is a group R₁₂ as above defined or a group C₁₋₃ alkyl, C₁₋₃ alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO₂, NH₂, CN, CH₃, Cl, Br;

R₅, R₆, R₇, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group; with the proviso that when R₁ or R₂ are benzyl or 4-hydroxybenzyl then R₃ and R₄ are isopropyl and an acceptable salt or enantiomer thereof] f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R₁ and R₂ which may be the same or different from one another, represent the side chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenylalanine, either mono- or di-substituted with residues selected from the group consisting of C₁₋₃ alkyl or halo-alkyl, C₁₋₃ alkoxy or amino-alkoxy, halogen, OH, NH₂ and NR₁₃R₁₄, where R₁₃ and R₁₄, which may be the same or different from one another, represent a hydrogen or C₁₋₃ alkyl group;

R₃ is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with n = 1-5 (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or

alkylcycloalkyl of formula C_nH_{2n-1} with $n = 5-9$ (selected from the group consisting of: cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r-Ar_1$, where $r = 1$ or 2 and where Ar_1 is an aromatic group selected from the group consisting of: α -naphthyl, β -naphthyl, phenyl, indole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of: C_{1-3} alkyl, CF_3 , C_{1-3} alkoxy, Cl, F, OH and NH_2 ;

R_4 represents an L-Q group where:

L is a chemical bond or CH_2 , and

Q is selected from the group consisting of:

$-OH$, NH_2 , NR_9R_{10} , OR_{11} , and where R_9 and R_{10} , which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, C_{1-3} hydroxy alkyl, C_{1-3} dihydroxyalkyl, C_{1-3} alkyl- $CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine, galactosamine, N-acetylglucosamine and N-acetylgalactosamine, C_{1-3} alkyltetrazole, C_{1-3} alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain; $NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, C_{1-6} alkyl chain containing a polar group (chosen in the group consisting of NH_2 , COOH, $CONHR_{12}$, (wherein R_{12} is as hereabove defined) or ([1,4']bipiperidine) $-COOH$, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl.

$-R_5$, R_6 , R_7 are H,

in which the carbon atom that carries the substituents R_3 and R_7 has configuration R.

3. (Amended three times) A compound according to Claim 2 selected from:

- (a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)- CH_2 -NH]}
- (b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)- CH_2 -NH]}
- (c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)- CH_2 -NH]}
- (d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4(4-OCH_3)$)- CH_2 -NH]}
- (e) Cyclo{-Suc-Trp(5F)-Phe-[(R)-NH-CH($CH_2C_6H_5$)- CH_2 -NH]}

- (f) Cyclo{-Suc-Trp(Me)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (h) Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH(CH₂C₆H₅)-CH₂-NH]}
- (j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₃-3,4-diCl)-CH₂-NH]}
- (k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂C₆H₄-4-OH)-CH₂-NH]}
- (l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-CH₂-C₆H₅)-CH₂-NH]}
- (m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-2-naphthyl)-CH₂-NH]}
- (n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-indol-3-yl)-CH₂-NH]}
- (o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-5-F-indol-3-yl)-CH₂-NH]}
- (p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-3-F)-CH₂-NH]}
- (q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₃-3,4-diF-CH₂-NH)-]}
- (r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₄-4-CF₃-CH₂-NH)-]}
- (s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (t) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH₂-CH(CH₂C₆H₅)-NH]}
- (u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-(CH₂)₃CO-}
- (v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-N(CH₃)]-(CH₂)₃CO-}
- (w) Cyclo{-Suc[1(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (x) Cyclo{-Suc[1(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (y) Cyclo{-Suc[2(S)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (z) Cyclo{-Suc[2(R)-NH₂]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (aa) Cyclo{-Suc[1(S)-NH(CH₃)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ab) Cyclo{-Suc[1-COO(CH₂-C₆H₄-4-NO₂)]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- [Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}]
- (ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]}
- (ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoro-acetic acid

- (ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ai) Cyclo{-Suc[1(S)-N(CH₃)₂]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (aj) Cyclo{-Suc[1(S)-(piperidin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ak) Cyclo{-Suc[1(S)-(N(CH₂CH₂OH)₂)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (al) Cyclo{-Suc[1(S)-(N(CH₂CH(OH)CH₂OH)]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.
- (an) Cyclo{-Suc[1(S)-[3-N'-β-D-glucopiranos-1-yl]-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-CH(CH₂-C₆H₅)-CH₂NH]-}
- (ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (ap) Cyclo{-Suc[1(S)-[N'-β-D-glucopiranos-1-yl]-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (aq) Cyclo{-Suc[1(S)-(chiny)amine]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}
- (ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-} trifluoroacetic acid
- (at) Cyclo{-Suc[1-N-(β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}; and
- (au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH₂-C₆H₅)-CH₂-NH]-}.

5. (Amended twice) A composition comprising a compound of general formula (I) according to Claim 1 in combination with a suitable carrier or excipient.[.]

9. (Amended twice) A composition according to claim 7, adapted for use as an anxiolytic[s].

12. (Amended twice) A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor in said mammal with a compound according to Claim 1 for a time and under conditions effective to antagonize [an] said NK-2.

13. (Amended twice) A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize [an] said NK-2 receptor.

14. (Amended twice) A method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and if the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting of a compound of formula (I), according to Claim 1, are administered to the patient for a time and under conditions effective to antagonize an NK-2 receptor.